AS Cont.

wherein said binding agent is at least one of a binding agent selected from the group consisting of a liposome, a polyamine, a siliceous compound, a zeolite, a polystyrene, chitin, and chitosan.

REMARKS

The present invention relates to novel nucleic acid reference standards and methods and kits relating thereto.

Claims 1-32 are pending in the present application. Claims 12-22 were withdrawn previously as being drawn to non-elected inventions, and claims 1-11 and 23-32 are under examination. Claims 2, 11, and 24 have been canceled herein without prejudice to the inclusion of any subject matter recited therein in any subsequent application.

Claims 1, 25 have been amended herein. Support for these amendments is found throughout the specification as filed as more fully set forth below. Therefore, no new matter has been added by way of these amendments.

Objections to Drawings

The Examiner has objected to Figure 3 in that, in her opinion, the numbering depicted in the figure is not clearly visible. Applicants, while not necessarily agreeing with the Examiner, in a good faith effort to expedite prosecution of this application, have amended Figure 3 to render the lane numbering more visible in the drawing. No new matter has been added by way of this amendment, which serves merely to add more visible numbering. A "marked-up" copy of Figure 3 indicating the changes made thereto is enclosed herewith, as is a "clean" substitute version of the drawing incorporating the changes.

The Examiner has also objected to Figure 7 in that, in her view, since there are 9 sample lanes in Figure 7, and 14 sample lanes depicted in Figure 6, the statement in the specification that the samples in both Figures are similar is not supported by the drawings. Applicants respectfully submit that the drawings support the statement. Nonetheless, in a good faith effort to expedite prosecution of this application, Applicants have relabeled Figure 7, and included a "marked-up" copy indicating changes thereto, to indicate all of the lanes some of which were not labeled in the figure as filed. Applicants respectfully submit that this amendment adds no new matter in that it serves merely to number lanes depicted in Figure 7 that were not previously numbered.

Additionally, Applicants respectfully submit that there is nothing unclear about Figures 7 and 8, as filed. This is because the specification as filed, at the detailed description at page 15, lines 8-16, and at page 70, line 8, to page 71, line 9, discloses that whether the DNA was extracted using the Gentra Puregene method (Figure 6), the QIAgen spin column method (Figure 7), or the standard phenol/chloroform method (Figure 8), a similar signal was obtained from the genetic test such that the nucleic acid reference standard demonstrated broad utility and applicability regardless of the extraction method used to process the sample.

Applicants do not understand the Examiner's assertion that at no place does the specification describe the samples shown in Figures 7 and 8. This is because it is clear that the data disclosed in Figures 7 and 8 are discussed at page 70, line 8, to page 71, line 9, where the various extraction methods (*i.e.*, Gentra Puregene, QIAgen spin column, and phenol/chloroform extraction) are compared using the FV DNA segment as assayed using a PCR based detection assay. This disclosure, when viewed in light of the specification in its entirety, including the figures and the detailed descriptions thereof, make it abundantly clear that the reference standard of the invention can be used in a variety of extraction methods demonstrating the standard's broad utility.

The skilled artisan, armed with the teachings of the invention in light of the skill in the art, would not have understood that Figures 7 and 8 failed to show that the samples were similar to those depicted in Figure 6 in that whether the reference standard was purified by Gentra Puregene, QIAgen spin column, and/or phenol/chloroform extraction, it gave the same results using the PCR-based detection method. These results are discussed at, *inter alia*, pages 70-71 and no more is required for purposes of 37 CFR 1.83(a). Thus, Applicants respectfully submit that Figures 7 and 8 and in no way unclear and that the objection to these figures should be reconsidered and withdrawn.

Objection to the Specification for reciting browser-executable code

The Examiner, at page 3 of the Office Action, has objected to the specification because it contains embedded hyperlink and/or other form of browser-executable code. Applicants, in a good faith effort to expedite the prosecution of this application, have removed any such code from pages 23 (line 28), 24 (line 12), and 38 (lines 15, 17, 18 and 22) of the specification. Applicants have deleted the paragraphs on each page containing the objected to text and have replaced them with a paragraph that does not contain the browser-executable code.

More specifically, Applicants have replaced the paragraphs commencing at page 23, line 20, and ending at page 24, line 13, and the paragraph commencing on page 38, line 2, and ending at line 22. A "marked-up" copy of each paragraph deleted and replaced, indicating the amendments made thereto, is attached hereto. These amendments add no new matter, but serve only to delete code that has been objected to by the Examiner.

Rejection of Claims 1-11 and 23-32, under 35 U.S.C. § 112, first paragraph

Claims 1-11 and 23-32 stand rejected under 35 U.S.C. § 112, first paragraph, because in the Examiner's opinion, while enabling for a target DNA bound to nylon, polystyrene, silica gel, liposome, aminopropyl glass or low alumina zeolyte particles in a solution comprising ethanol or acetate + isopropanol, the specification does not enable all types of nucleic acids bound to all possible types of microparticles in all possible solutions. Applicants respectfully submit that the claimed nucleic acid reference standard recited by claims 1-11 and 23-32 is enabled by the specification as filed under the current law pursuant to 35 U.S.C. § 112, first paragraph, for the following reasons.

It is well-settled that an Applicant need not have actually reduced the invention to practice prior to filing. MPEP §2164.02 (citing *Gould v. Quigg*, 822 F.2d 1074 (Fed. Cir. 1987)). Indeed, the invention need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation. *In re Borkowski*, 422 F.2d 904, 908 (C.C.P.A. 1970). The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. MPEP §2164.01 (citing *In re Angstadt*, 537 F.2d 498, 504 (C.C.P.A. 1976)).

The fact that experimentation may be complex does not necessarily make it undue if the art typically engages in such experimentation. *Id.* Further, the specification need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known to those skilled and already available to the public. MPEP §2164.05(a) (citing *In re Buchner*, 929 F.2d 660, 661 (Fed. Cir. 1991)). Therefore, under current law, enablement does not require a working example and experimentation is allowed so long as it is not undue.

Applicants respectfully submit that even though a working example is not required, the specification as filed sets forth numerous examples where the nucleic acid standard was reduced to practice. In these many examples, Applicants demonstrated that a wide plethora of microparticles can be used to produce the reference standard. These include, but are not

limited to, nylon, amine modified polystyrene (at page 64), liposomes (page 65), silica gel (page 68), aminopropyl glass (page 71), fumed silica and chitosan (page 73), and low alumina zeolite (page 77). Based on this ample reduction to practice, where the law does not require any reduction to practice, Applicants respectfully submit that the specification as filed provides enablement for a nucleic acid reference standard bound with a broad spectrum of microparticles encompassing, at the very least, those recited in claims 2 and 25, *i.e.*, a liposome, a polyamine, a siliceous compound, a zeolite, a polystyrene, chitin, an chitosan.

Accordingly, while not necessarily agreeing with the Examiner's reasoning, Applicants, in a good faith effort to expedite prosecution of this application, have amended claims 1 and 24 to recite the microparticles previously recited in claims 2 and 25 and have cancelled claims 2 and 25 herein. Applicants respectfully submit that the microparticles recited in claims 1 and 24, as amended, are amply enabled by the disclosure provided in the specification as filed. Therefore, Applicants respectfully submit that claims 1, 3-11, 23-24, and 26-32, as amended, are amply enabled by the specification as filed and the rejection of these claims under 35 U.S.C. § 112, first paragraph, should be reconsidered and withdrawn.

Applicants respectfully submit that the specification demonstrates that a wide variety of solutions were used, including, but not limited to, solutions comprising ethanol or acetate:isopropanol. These solutions include, among others, sodium acetate (page 54), deionized water (page 65), chaotropic salts (*e.g.*, sodium idodide; page 66), ethanol (page 67), guanidium hydrochloride (page 71), sodium acetate:acetic acid:isopropanol (page 73), and isopropanol:acetate (page 74). Accordingly, where such extensive reduction to practice is demonstrated setting forth such a wide plethora of solutions, the specification as filed supports the solutions recited in claims. This is especially true where one skilled in the art would have appreciated, based upon the disclosure provided in the specification as filed, that the solution used depended on the microparticle being used to prepare the reference standard. Further, the patent law does not require that every single combination of microparticle and solution be reduced to practice where the art typically performed such experimentation and where the specification discloses numerous examples where broad types of microparticles and a wide variety of solutions had been reduced to practice. Thus, any experimentation required to practice the invention within the scope of the claims as now amended was clearly not undue to one skilled in the art armed with the teachings of the invention. Therefore, where not even one working example is required for enablement under 35 U.S.C. §112, first paragraph, the Examiner

is apparently demanding that each and every microparticle and/or solution must first be reduced to practice before the claimed standards can be patented. Applicants respectfully submit that this is simply not the law under the patent statute.

The law is well-settled that extensive experimentation is not undue if one of ordinary skill in the art routinely engages in such experimentation. Further, the high degree of skill in the art, the extensiveness of experimentation routinely performed by the artisan, and that one skilled in the art of reference standards typically engaged in this type of experimentation at the time the application was filed must be considered. This is important, since the present case law regarding enablement under 35 U.S.C. §112, first paragraph, allows significant experimentation without finding it undue if the art typically engages in such experimentation.

Moreover, under the present law of enablement, generic claims reciting large numbers of species are allowable without disclosure of every species so long as the art engages in experimentation to identify the operative species encompassed by the generic claim. In *In re Vaeck* , 20 USPQ2d 1438, 1445 (Fed. Cir. 1991), reviewing an enablement rejection of a broad claim reciting methods for producing insect proteins in cyanobacteria, the Court of Appeals for the Federal Circuit discussed enablement in the context of generic species claims:

> we do not imply that patent applicants in art areas currently denominated as "unpredictable" must never be allowed generic claims encompassing more than the particular species disclosed in their specification. It is well settled that patent applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art. *In re Angstadt*, 537 F.2d 498, 502-03, 190 USPQ 214, 218 (CCPA 1976). However, there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and how to use the invention as broadly as it is claimed. This means that the disclosure must adequately guide the art worker to determine, without undue experimentation, which species among all those encompassed by the claimed genus possess the disclosed utility.

In re Vaeck, 20 USPQ2d at 1445 (emphasis added). Thus, not every species need be disclosed where one skilled in the art would be able, without undue experimentation, to determine which species possess the disclosed utility. *See also In re Druey*, 145 USPQ 219, 221 (Bd. Pat. App. & Int. 1965)("The fact that not all possible substituents encompassed by the generic language are illustrated does not preclude appellants from asserting the genus when no reasons have been advanced by the examiner to rebut appellants' assertion that all the compounds

embraced by the genus will in fact have the properties ascribed to them."). Thus, each particular microparticle and each particular solution need not be reduced to practice before the present claims are enabled.

The MPEP at § 2164.08(b), discussing inoperative subject matter, states:

> The presence of inoperative embodiments within the scope of a claim does not necessarily render a claim non-enabled. The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art. *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 224 USPQ 409, 414 (Fed. Cir. 1984) (prophetic examples do not make the disclosure nonenabling.
> . . . A disclosure of a large number of operable embodiments and the identification of a single inoperative embodiment did not render a claim broader that the enabled scope because undue experimentation was not involved in determining those embodiments that were operable. *In re Angstadt*, 190 USPQ 214, 218 (CCPA 1976).

Thus, inoperative embodiments do not necessarily render a claim nonenabled as long as the experimentation required to identify the operative species is not undue.

In the landmark enablement case of in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988), the court discussed the adequacy of disclosure with regard to a patent disclosing an immunoassay method for the detection of hepatitis B antigen using monoclonal antibodies. The *Wands* Court noted that of 143 hybridomas produced, only nine were assayed and, of those, only four hybridomas secreted IgM antibodies and exhibited a binding affinity constant for the HBsAg determinants of at least 10^9 M^{-1}, a "respectable 44 percent rate of success." *In re Wands*, 8 USPQ2d at 1406. Finding the claims were enabled, the *Wands* Court stated:

> Wands' disclosure provides considerable direction and guidance on how to practice their invention and presents working examples. There was a high level of skill in the art at the time when the application was filed, and all of the methods needed to practice the invention were well known .
> The nature of monoclonal antibody technology is that it involves screening hybridomas to determine which ones secrete antibody with desired characteristics. Practitioners of this art are prepared to screen negative hybridomas in order to find one that makes the desired antibody. No evidence was presented by either party on how many hybridomas would be viewed by those in the art as requiring undue experimentation to screen.

In re Wands, 8 USPQ2d at 1406 (emphasis added). Therefore, where, as here, the art typically screens a wide variety of microparticles, and where a wide plethora of solutions where routinely assayed by the skilled artisan, one skilled in the art would not require undue experimentation to practice the invention commensurate with the scope of claims 1, 3-11, 23-24, and 25-32 without undue experimentation. Thus, where one skilled in the art routinely assays microparticles and solutions to produce reference standards as disclosed in the specification as filed, having to do so is not the undue experimentation proscribed by 35 U.S.C. § 112, first paragraph, under the reasoning of *In re Wands*.

In *In re Angstadt*, 190 USPQ 214 (CCPA 1976), the court addressed the level of experimentation in an unpredictable art, *i.e.*, the chemical arts, where the claimed invention involved a method of catalytically producing hydroperoxides where the specification admitted that not all disclosed complexes produced the hydroperoxides. The *Angstadt* Court, holding that the invention as claimed was enabled, reasoned:

> We note that many chemical processes, and catalytic processes particularly, are unpredictable. . . .
>
> Appellants have apparently not disclosed every catalyst which will work; they have apparently not disclosed every catalyst which will not work. The question, then, is whether in an unpredictable art, section 112 requires disclosure of a test with every species covered by a claim. To require such a complete disclosure would apparently necessitate a patent application or applications with "thousands" of examples or the disclosure of "thousands" of catalysts along with information as to whether each exhibits catalytic behavior resulting in the production of hydroperoxides. More importantly, such a requirement would force an inventor seeking adequate patent protection to carry out a prohibitive number of actual experiments. This would tend to discourage inventors from filing patent applications in an unpredictable area since the patent claims would have to be limited to those embodiments which are expressly disclosed. A potential infringer could readily avoid "literal" infringement of such claims by merely finding another analogous catalyst complex which could be used in "forming hydroperoxides."

In re Angstadt, 190 USPQ at 218 (emphasis added) (citations omitted). Similarly, in *In re Bundy*, 209 USPQ 48, 52 (CCPA 1981), the court noted the public policy reasons mitigating against imposing a requirement that each compound be tested before a generic species claim would is allowed:

> Early filing of an application with its disclosure of novel compounds which possess significant therapeutic use is to be encouraged. Requiring specific testing of the thousands of prostaglandin analogs encompassed by the present claim in order to satisfy the how-to-use requirement of § 112 would delay disclosure and frustrate, rather than further, the interests of the public.

Thus, where methods for assessing the effectiveness of a reference nucleic acid are disclosed in the specification and where a wide variety of microparticles and solutions is extensively disclosed and reduced to practice in the specification as filed, it would not be undue experimentation to use a variety of microparticles and solutions as disclosed in the present specification where the art typically engages in such experimentation.

More recently, in *Ex parte Mark*, 12 USPQ2d 1904 (Bd. Pat. App. & Int. 1989), the Board reversed the Examiner's rejection for lack of enablement under 35 U.S.C. § 112, first paragraph, with regard to an application involving admittedly "innumerable" muteins (*i.e.*, mutated protein variants of the naturally-occurring protein) comprising a non-essential cysteine which exhibit biological activity after modification to substitute the cysteine. In reversing the Examiner, the *Mark* Court stated:

> To the extent that the examiner is concerned that undue experimentation would be required to determine other proteins suitable for use in the present invention, we find [an applicant]'s declaration to be persuasive that only routine experimentation would be needed for one skilled in the art to practice the claimed invention for a given protein. The fact that a given protein may not be amenable for use in the present invention in that the cysteine residues are needed for the biological activity of the protein does not militate against a conclusion of enablement. One skilled in the art is clearly enabled to perform such work as needed to determine whether the cysteine residues of a given protein are needed for retention of biological activity.

Ex parte Mark, 12 USPQ2d at 1907. Therefore, where one skilled in the art routinely assays the compounds for the asserted utility, it is not undue experimentation for them to do so. Similarly, where the invention discloses a large number of microparticles and solutions, not every microparticle or solution must be successfully used to produce a reference standard according to the teachings of the invention before such reference standards can be patented.

In addition, Applicants do not understand the Examiner's assertion that RNA standards are not enabled by the specification as filed. The art is replete with teachings as to how to effectively prepare solutions comprising stable RNA and RNA is known to bind to microparticles similarly to the binding of DNA to those particles. Thus, the specification as filed amply supports claims relating to stable RNA reference standards, and the rejection under 35 U.S.C. §112, first paragraph, based on lack of enablement of RNA standards should be reconsidered and withdrawn.

The specification as filed amply supports that the claimed standards are enabled under 35 U.S.C. §112, first paragraph, and the rejection of claims 1, 3-11, 23-24, and 26-32, should be reconsidered and withdrawn.

Rejection of claims 1-11, and 23, pursuant to 35 U.S.C. §112, second paragraph

Claims 1 and 2, and claims depending therefrom, stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. In the Examiner's opinion, claims 1 is indefinite for reciting "stable isolated nucleic acid reference standard." Applicants respectfully submit that claim 1, as amended, is not indefinite in any way. Applicants do not understand the Examiner's contention that a definition of "stable" was not provided. Applicants defined "stable" at page 33, lines 4-8, in that the standard "can be maintained at room temperature for a prolonged period without significant loss of signal when the presence of a nucleic acid present in the standard is assessed compared with the identical nucleic acid which is not bound with a binding agent." Thus, the term "stable" as it pertains to the reference standard is explicitly defined in the specification as filed and the term is exemplified in the numerous examples provided as the specification demonstrated extensive reduction to practice of the standard.

It is settled law that the "patent law allows the inventor to be his own lexicographer." *Chicago Steel Foundry Co. v. Burnside Steel Foundry Co.*, 132 F.2d 812 (7th Cir. 1943). *See also* MPEP § 2173.01. This is because "[t]he dictionary does not always keep abreast of the inventor. It cannot. Things are not made for the sake of words, but words for things." *Autogiro Co. v. U.S.*, 155 USPQ 697 (Ct. Cls. 1967). Further, applicant is entitled to have the claims construed in connection with the other parts of the application. *See Autogiro Co. v. U.S.*, 155 USPQ 697 (Ct. Cls. 1967). Therefore, Applicants are entitled to define terms to describe their invention and the claims must be interpreted in light of the other parts of the application including the disclosure in the specification and the definitions provided therein.

Applicants respectfully submit that the specification as filed makes clear that "stable isolated nucleic acid reference standard" is compared to the stability of the nucleic acid portion of the standard in the absence of the binding agent portion of the standard. The patent law does not proscribe the definition of a term based on a relative comparison. Thus, the standard is properly defined as "stable" by comparing the loss of signal of the nucleic acid in the absence of the binding agent to the loss of signal of the nucleic acid which is combined with the binding agent. Thus, the form of the standard (*e.g.*, dried or in solution) is not essential for purposes of the definition, since the definition makes it clear that the standard is more stable than an otherwise identical nucleic acid that is treated similarly to the nucleic acid bound with a binding agent.

Similarly, the assay conditions for assessing the level of signal is not important where Applicants' definition makes clear that the samples are compared and treated identically except the reference standard is compared to an otherwise identical nucleic acid that is not bound with a binding agent which is treated identically to the reference standard being assessed. One skilled in the art would have appreciated, based upon the disclosure provided in the specification as filed, that the precise storage conditions and assay used to compare the standard to the otherwise identical nucleic acid in the absence of the binding agent was not important, only the relative comparison matters. Thus, the term "stable isolated nucleic acid reference standard", which is explicitly defined in the specification at page 33, and which is extensively exemplified throughout the specification as filed, would have been well understood by one skilled in the art and is not vague or indefinite in any way. Accordingly, Applicants respectfully request that the rejection of claim 1 under 35 U.S.C. § 112, second paragraph, for indefiniteness be reconsidered and withdrawn.

The Examiner further contends that claim 1 is indefinite for reciting "target nucleic acid is not substantially detectable in a nucleic acid assay." The Examiner asserts that the phrase is unclear because it is unclear in what type of nucleic acid assays the standard will be undetectable. Applicants respectfully submit that claim 1, as amended, is not indefinite in any way in that, as discussed previously with regard to the term "stable", Applicants have explicitly set forth what is meant by "substantially detected" means in a nucleic acid assay. More specifically, at page 33, lines 13-26, Applicants made it abundantly clear that "substantially detected" means that the target nucleic acid is either not detected, or detected at a lower level, compared with an otherwise identical target nucleic acid which is not bound with a binding

agent. Thus, the particular assay employed is not important for purposes of this definition. Rather, the relative signal detected, or not, when the reference standard is compared with an otherwise identical target nucleic acid not bound with the binding agent is what is used to determine whether the target nucleic acid is or is not substantially detected in a nucleic acid standard, and this term would have been clearly understood by one skilled in the art armed with the teachings of the invention. Therefore, claim 1 is not vague or indefinite in any way, and the rejection under 35 U.S.C. § 112, second paragraph, should be reconsidered and withdrawn.

The Examiner rejected claim 2 as being indefinite. However, claim 2 having been canceled herein has rendered this rejection moot.

Objection to claim 11, under 37 CFR 1.75

The Examiner has objected to claim 11, under 37 CFR 1.75, as being a substantial duplicate of claim 1. Applicants, while not necessarily agreeing with the Examiner's reasoning, and in a good faith effort to expedite prosecution of this application, have canceled claim 11, thereby rendering this objection moot.

Rejection of claims 1, 2, 8-11, pursuant to 35 U.S.C. §102(b)

Claims 1, 2, 8-11 stand rejected under 35 U.S.C. §102(b), as being anticipated by Hayashida et al. (1995, Gene 165:155-161). The Examiner reasons that Hayashida teaches latex-bound DNA that was stable for several months and which can be used for hybridization assays. Somehow, the Examiner opines that Hayashida teaches the reference nucleic acid standard of claim 1, and claims depending therefrom. Applicants respectfully submit that Hayashida does not anticipate the present invention for the following reasons.

Preliminarily, Applicants respectfully point out that claim 2 has been canceled herein and any rejection of this claim has now been rendered moot.

It is hornbook law that "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." MPEP §2131 (quoting *Verdegaal Bros. v. Union Oil Co. of Calif.*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987)). "The identical invention must be shown in as complete detail as is contained in the . . . claim." *Id.* (quoting *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989) (emphasis added). Therefore, Hayashida must describe each and every

element of claims 1, 8-11, in order to anticipate these claims under Section 102(b), and this reference does not.

Hayashida teaches binding large segments of DNA to latex particles and then using the DNA thus bound to isolated nucleic acids encoding sequences complementary to the DNA bound to the particles. This is demonstrated in Figure 2, at page 157, wherein the DNA bound to the latex particles was used for hybridization selection. The nucleic acids of Hayashida, which are bound with latex particles, cannot possibly anticipate the nucleic acid reference standard of claim 1, and claims depending therefrom, in that the target nucleic acid portion of Applicants' reference standard cannot be substantially detected in a nucleic acid assay such as, but not limited to, the hybridization selection of Hayashida.

Applicants note that the Examiner, at page 7 of the Office Action, has based his prior art rejections under 35 U.S.C. §§ 102 and 103 on a composition comprising a target nucleic acid and a microparticulate binding agent. That is, the Examiner decided to ignore the claim limitation that the "target nucleic acid is not substantially detected in a nucleic acid assay" because, in the Examiner's opinion, such limitation is unclear in that it is not clear in which assays the nucleic acid is not detected.

Again, Applicants respectfully point out that the term "substantially detected in a nucleic acid assay" is defined in the specification at page 33, lines 13-26. Moreover, the nucleic assays that are included within the definition are clearly exemplified throughout the specification as filed and would have been well-understood by the skilled artisan based upon the disclosure provided in the specification. Therefore, Applicants respectfully submit that this term cannot be ignored and that claim 1, when read in light of the specification as filed and in view of the understanding of one skilled in the art, is not unclear in any way.

When claim 1 is read in its entirety, encompassing the limitation that the target nucleic acid is not substantially detected when it is bound with the binding agent, as it must be when the claim is read in light of the specification as required by current patent law, Hayashida cannot anticipate the present invention. This is because, as demonstrated by Figure 2 of Hayashida, at page 157, the target nucleic acid (*i.e.*, λ DNA) is clearly substantially detected (*i.e.*, by hybridization selection) while bound with the binding agent (*i.e.*, latex particles). Therefore, Hayashida, where the target nucleic acid is readily detectable using a nucleic acid assay (*e.g.*, hybridization selection) cannot anticipate the present invention as recited in claims 1, and 8-11, and the rejection under 35 U.S.C. §102(b) should be reconsidered and withdrawn.

Hayashita also cannot render the present invention obvious in further view of the Stratagene Catalog. This is because the catalog, which merely teaches the availability of various kits, cannot correct the deficiencies of Hayashita. More specifically, the MPEP states, in relevant part:

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all of the claim limitations. MPEP § 2142.

None of these requirements has been satisfied in the instant matter where Hayashita, combined with the Stratagene catalog, does not teach or suggest all the claim limitations. Also, there would have been no motivation to combine these references, nor any expectation of success that doing so would arrive at the present invention.

Therefore, Hayashita, in view of the Stratagene catalog, cannot render the claims *prima facie* obvious and this rejection under 35 U.S.C. §103(a) should be reconsidered and withdrawn.

Rejection of claims 1, 2, 5, 8-11, 23-25, 28, 31, and 32, pursuant to 35 U.S.C. §102(b)

Claims 1, 2, 8-11 stand rejected under 35 U.S.C. §102(b), as being anticipated by van Gemen et al. (1995, PCR Primer: A Laboratory Manual, Cold Spring Harbor Lab. Press, pp. 667-677). The Examiner reasons that Van Gemen teaches a nucleic acid in which genomic HIV-1 RNA is bound to silica together with three RNA internal standards. Somehow, the teachings of Van Gemen anticipate the present invention in the Examiner's view.

However, Van Gemen does not teach a reference standard at all. Rather, Van Gemen merely teaches binding RNA to silica and eluting the RNA which is then assayed for the presence of a target nucleic acid. This is clearly not Applicants' standard as recited by claim 1 and claims depending therefrom. Therefore, Van Gemen cannot anticipate the present invention.

Van Gemen also cannot render the present invention obvious in further view of the Stratagene Catalog. This is because the catalog, which merely teaches the availability of

various kits, does not make up for the deficiencies of Van Gemen. Therefore, Van Gemen, in view of the Stratagene catalog, cannot render the claims prima facie obvious and this rejection under 35 U.S.C. §103(a) should be reconsidered and withdrawn.

Rejection of claims 1, 2, 8-11, pursuant to 35 U.S.C. §102(b) and §103(a)

Claims 1, 2, 8-11 stand rejected under 35 U.S.C. §§102(b) and 103(a), as being anticipated, and/or in the alternative, rendered obvious, by Hayatsu et al. (1997, Chem Pharm. Bull. 45:1363-1368). The Examiner reasons that Hayatsu teaches genomic DNA bound to chitosan thereby anticipating or rendering obvious the reference nucleic acid standard of claim 1, and claims depending therefrom. Applicants respectfully submit that Hayatsu does not anticipate the present invention for the following reasons.

Preliminarily, Applicants respectfully point out that claim 2 has been canceled herein and any rejection of this claim has now been rendered moot.

Hayatsu, like Hayashida teaches binding large DNA to particles and then using the DNA thus bound to isolated nucleic acids encoding sequences complementary to the DNA bound to the particles. The nucleic acids of Hayatsu, cannot possibly anticipate the nucleic acid reference standard of claim 1, and claims depending therefrom, in that the target nucleic acid portion of Applicants' reference standard cannot be substantially detected in a nucleic acid assay.

As previously pointed out , the Examiner, at page 7 of the Office Action, has based his prior art rejections under 35 U.S.C. §§ 102 and 103 on a composition comprising a target nucleic acid and a microparticulate binding agent, ignoring the claim limitation that the "target nucleic acid is not substantially detected in a nucleic acid assay". This is not proper under the present patent laws and the claim limitation cannot be ignored.

When claim 1 is read in its entirety, encompassing the limitation that the target nucleic acid is not substantially detected when it is bound with the binding agent, as it must be when the claim is read in light of the specification as required by current patent law, Hayatsu does not anticipate the present invention and the rejection under 35 U.S.C. §102(b) should be reconsidered and withdrawn.

Hayatsu also cannot render the present invention obvious in further view of the Stratagene Catalog. This is because the catalog, which merely teaches the availability of various kits, cannot correct the deficiencies of Hayatsu. That is, Hayatsu, combined with the Stratagene catalog, does not teach or suggest all the claim limitations. Also, there would have been no

motivation to combine these references, nor any expectation of success that doing so would arrive at the present invention.

Therefore, Hayatsu, in view of the Stratagene catalog, cannot render the claims *prima facie* obvious and this rejection under 35 U.S.C. §103(a) should be reconsidered and withdrawn.

Rejection of claims 1, 2, 8-11, pursuant to 35 U.S.C. §102(b) and §103(a)

Claims 1, 2, 8-11 stand rejected under 35 U.S.C. §§102(b) and 103(a), as being anticipated, and/or in the alternative, rendered obvious, by Kariko et al. (1998, Biochim. Biophys. Acta 1369:320-334). The Examiner reasons that Kariko teaches a nucleic acid bound to liposomes thereby anticipating or rendering obvious the reference nucleic acid standard of claim 1, and claims depending therefrom. Applicants respectfully submit that Kariko does not anticipate the present invention for the following reasons.

Preliminarily, Applicants respectfully point out that claim 2 has been canceled herein and any rejection of this claim has now been rendered moot.

Kariko, like Hayashida teaches binding nucleic acids to a binding agent and then using the nucleic acids thus bound to transfect cells. The nucleic acids of Kariko cannot possibly anticipate the nucleic acid reference standard of claim 1, and claims depending therefrom, in that the target nucleic acid portion of Applicants' reference standard cannot be substantially detected in a nucleic acid assay while there is nothing in Kariko to suggest that the nucleic acids disclosed therein would not be substantially detected.

As previously pointed out , the Examiner, at page 7 of the Office Action, has based his prior art rejections under 35 U.S.C. §§ 102 and 103 on a composition comprising a target nucleic acid and a microparticulate binding agent, ignoring the claim limitation that the "target nucleic acid is not substantially detected in a nucleic acid assay". This is not proper under the present patent laws and the claim limitation cannot be ignored.

When claim 1 is read in its entirety, encompassing the limitation that the target nucleic acid is not substantially detected when it is bound with the binding agent, as it must be when the claim is read in light of the specification as required by current patent law, Kariko does not anticipate the present invention and the rejection under 35 U.S.C. §102(b) should be reconsidered and withdrawn.

Kariko also cannot render the present invention obvious in further view of the Stratagene Catalog. This is because the catalog, which merely teaches the availability of various kits, cannot correct the deficiencies of Kariko. That is, Kariko, combined with the Stratagene catalog, does not teach or suggest all the claim limitations. Also, there would have been no motivation to combine these references, nor any expectation of success that doing so would arrive at the present invention.

Therefore, Kariko, in view of the Stratagene catalog, cannot render the claims *prima facie* obvious and this rejection under 35 U.S.C. §103(a) should be reconsidered and withdrawn.

Summary

Applicants respectfully submit that each rejection of the Examiner to the claims of the present application has been either overcome or is now inapplicable, and that each of claims 1, 3-10, 12-24, 26-32, is in condition for allowance. Reconsideration and allowance of each of these claims are respectfully requested at the earliest possible date.

Respectfully submitted,

CLARK RUNDELL *ET AL.*

May 27, 2003
Date

By: _____
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Encs. (Petition for Extension of Time and fee therefor; "marked-up" copy of paragraphs amended)

"Marked-up" copy of Paragraph at page 23, line 20, to page 24, line 6

The determination of percent identity between two nucleotide or amino acid sequences can be accomplished using a mathematical algorithm. For example, a mathematical algorithm useful for comparing two sequences is the algorithm of Karlin and Altschul (1990, Proc. Natl. Acad. Sci. USA 87:2264-2268), modified as in Karlin and Altschul (1993, Proc. Natl. Acad. Sci. USA 90:5873-5877). This algorithm is incorporated into the NBLAST and XBLAST programs of Altschul, et al. (1990, J. Mol. Biol. 215:403-410), and can be accessed, for example, at the National Center for Biotechnology Information (NCBI) world wide web site [having the universal resource locator "http://www.ncbi.nlm.nih.gov/BLAST/"]. BLAST nucleotide searches can be performed with the NBLAST program (designated "blastn" at the NCBI web site), using the following parameters: gap penalty = 5; gap extension penalty = 2; mismatch penalty = 3; match reward = 1; expectation value 10.0; and word size = 11 to obtain nucleotide sequences homologous to a nucleic acid described herein. BLAST protein searches can be performed with the XBLAST program (designated "blastn" at the NCBI web site) or the NCBI "blastp" program, using the following parameters: expectation value 10.0, BLOSUM62 scoring matrix to obtain amino acid sequences homologous to a protein molecule described herein.

"Marked-up" copy of Paragraph at page 24, lines 7-13

To obtain gapped alignments for comparison purposes, Gapped BLAST can be utilized as described in Altschul et al. (1997, Nucleic Acids Res. 25:3389-3402). Alternatively, PSI-Blast or PHI-Blast can be used to perform an iterated search which detects distant relationships between molecules (*id.*) and relationships between molecules which share a common pattern. When utilizing BLAST, Gapped BLAST, PSI-Blast, and PHI-Blast programs, the default parameters of the respective programs (*e.g.*, XBLAST and NBLAST) can be used. *See* [http://www.ncbi.nlm.nih.gov.] world wide web site for the government National Center for Biotechnology Information, National Library of Medicine, National Institutes of Health.

"Marked-up" copy of Paragraph at page 38, lines 2-22

The skilled artisan would appreciate, based upon the disclosure provided herein, the wide plethora of nucleic acids can be used as a target nucleic acid to produce the nucleic acid reference standard of the invention. That is, virtually any nucleic acid sequence of interest can be introduced into the construct using the methods disclosed herein to produce the claimed reference standard. More specifically, the invention encompasses a nucleic reference standard comprising a wide plethora of target nucleic acids, including, but not limited to, a methyltetrahydrofolate reductase gene, a beta cystathionase synthetase nucleic acid, nucleic acid related to coagulation factors including Factor II, Factor VII, Factor VIII, and Factor IX, a nucleic acid associated with prothrombin, nucleic acid containing translocations related to hematologic disease including a BCR/abl nucleic acid, and other nucleic acids related to a genetic disease such as those listed in the GENETESTS® database maintained by Hanson et al. That is, many nucleic acid sequences associated with a disease, disorder or condition are described at [http://www.genetests.org] the world wide web site of the GeneTests organization, and the web site provides an extensive list of genetic diseases wherein a mutation has been identified that is associated with the disease [(http://www.geneclinics.org/profiles/disclaimer-index.html)] at the world wide web site of the GeneClinics organization, while the number of genetic diseases identified which are correlated to a known mutation(s) is expanding every day. Further, the target nucleic acid encompasses both wild type and mutation nucleic acid sequences of the CFTR gene including those set forth at the publicly available web site [http://www.genet.sickkids.on.ca/cftr] of the Department of Genetics, The Hospital for Sick Children, Ontario, Canada, which site is maintained by Lap-Chee Tsui et al.

"Marked-up" copy of claims amended

1. (Amended) A stable isolated nucleic acid reference standard, said nucleic acid reference standard comprising an isolated target nucleic acid comprising a known sequence wherein said isolated target nucleic acid is bound with a microparticulate binding agent, and wherein when said isolated target nucleic acid is so bound said isolated target nucleic acid is not substantially detected in a nucleic acid assay, wherein said binding agent is at least one of a binding agent selected from the group consisting of a liposome, a polyamine, a siliceous compound, a zeolite, a polystyrene, chitin, and chitosan.

24. (Amended) A kit for producing a nucleic acid reference standard, said kit comprising an isolated target nucleic acid comprising a known sequence and a binding agent, said kit further comprising an applicator, and an instructional material for the use thereof, wherein said binding agent is at least one of a binding agent selected from the group consisting of a liposome, a polyamine, a siliceous compound, a zeolite, a polystyrene, chitin, and chitosan.

FIG. 7

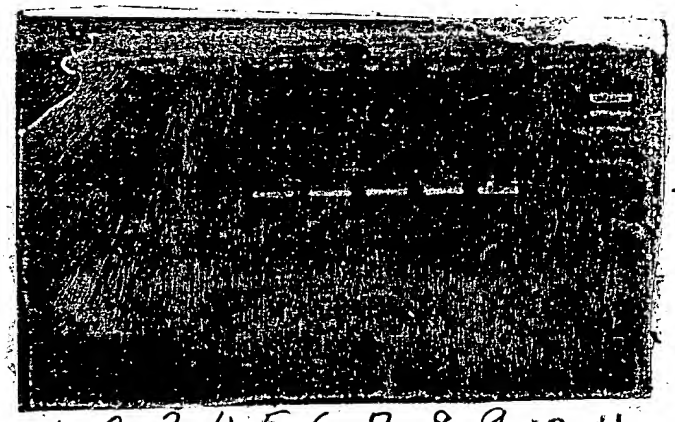

FIG. 8